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Asymmetric Addition of Grignard Reagents to Chiral 1-Acylpyridinium Salts: A Chiral Auxiliary Study

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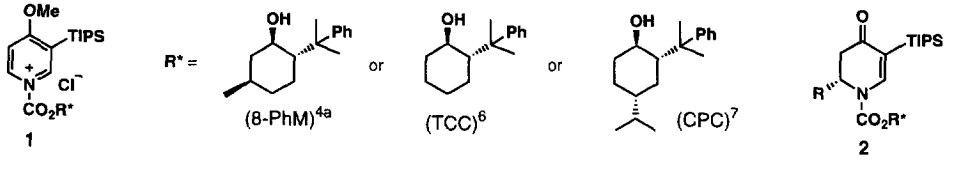
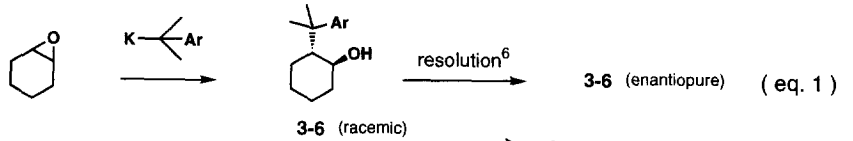
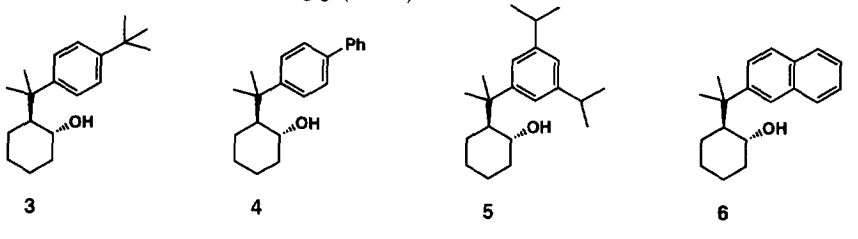
Abstract: *Various cyclohexyl-based chiral auxiliaries were studied for their effectiveness in the chiral 1-acylpyridinium salt/Grignard reaction.* Copyright © 1996 Elsevier Science Ltd

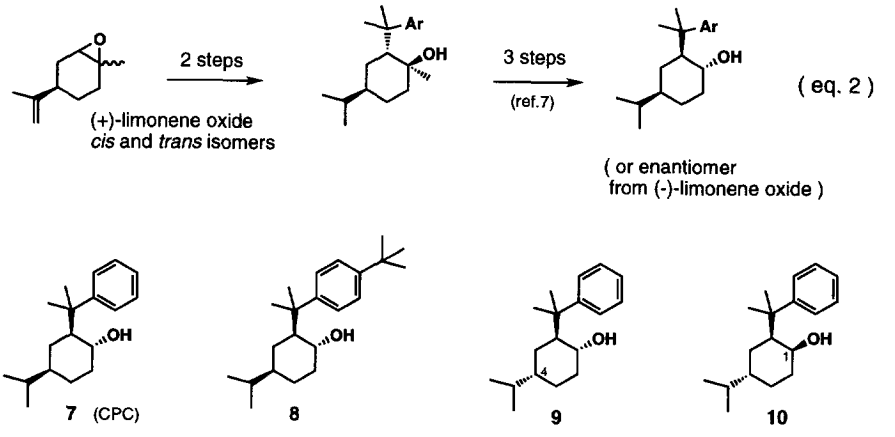
The addition of Grignard reagents[1] or metallo enolates[2] to homochiral 1-acylpyridinium salts of the type **1** provides synthetically useful *N*-acyl-2,3-dihydro-4-pyridones **2**. The potential of this methodology for the enantioselective synthesis of alkaloids is considerable.[3] Efforts are underway in our laboratories to explore the scope of this chemistry, to improve the degree of asymmetric induction, and to understand the factors involved in the transfer of chirality from the auxiliary. Cyclohexyl-based chiral auxiliaries of the 8-phenylmenthol type have proven to be very effective at providing high levels of stereo control in numerous asymmetric reactions.[4,5] The chiral inducing ability of the auxiliary can be increased



by modifying its aromatic ring, and several 8-arylmenthols have been prepared for this purpose.[5] Due to the success obtained with 8-phenylmenthol (8-PhM) and the related *trans*-2-(α-cumyl)cyclohexanol (TCC) as auxiliaries for the enantioselective formation of dihydropyridones **2**,[1,2] a project was initiated to study the effectiveness of various cyclohexyl-based chiral auxiliaries in the asymmetric 1-acylpyridinium salt/Grignard reaction. Herein are reported the initial results of this study.







Several of the chiral auxiliaries were synthesized by using methods previously developed in our laboratories. The *trans*-2-(1-methyl-1-arylethyl)cyclohexanols **3-6** were prepared from cyclohexene oxide and an isopropylarylpotassium (eq. 1).[6] The auxiliaries **7-10** are of the CPC type, and are readily available from (+)- or (-)-limonene oxide (eq. 2).[7] The C-1 epimer **10** was prepared by sodium borohydride reduction of the corresponding epi-CPC-ketone.[7]

The structure of the auxiliary's aryl appendage was chosen based on previous results reported for 8-phenylmenthyl derivatives. A 4-*tert*-butyl aryl substituent has been shown to be beneficial in 8-PhM-type auxiliaries by d'Angelo.[4c] Cyclohexyl-based auxiliaries containing the *p*-biphenyl aryl group have been shown to be effective by Whitesell for certain asymmetric reactions,[8] and the presence of a β-naphthylene has been found to be beneficial in several chiral auxiliaries and asymmetric catalysts.[4c,9]

Various Grignard reagents were added to chiral 1-acylpyridinium salts **1**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[1] and a chloroformate derived from a cyclohexyl-based chiral auxiliary. The results of this study are given in Table 1. Of the TCC derivatives (**3-6**), auxiliary **5** was the least effective giving diastereoselectivities of 83%. Auxiliaries **3, 4** and **6** gave de's in the range of 86-93%. The 2-naphthyl derivative **6,** shown by d'Angelo and coworkers to be an excellent auxiliary for certain conjugate addition reactions,[9] was approximately equivalent to **3** but not quite as effective as the biphenyl derivative **4.** Of these three, the 4-*tert*-butylphenyl derivative **3** is the easiest to prepare on a large scale.[6b]

In general, the *trans*-CPC-type auxiliaries **7-9** are more effective than the TCC derivatives. The *cis*- (α-cumyl)cyclohexanol **10** was examined with only phenyl Grignard, since the degree of asymmetric induction was practically nil (entry q). The auxiliary **10** was chosen for study based on Whitesell's[5] observation that the analogous *cis*-C1,2 isomer of 8-phenylmenthol induced chirality at the same level but in the opposite sense (vs. 8-PhM) during an asymmetric ene reaction. In contrast, it appears the chiral pyridinium salt **1** requires a *trans*-C1,2 configuration in the cyclohexyl-based[2] auxiliary for effective transfer of chirality. Again, the presence of a 4-*tert*-butyphenyl group in the auxiliary **(8)** proved to be beneficial. The C-4 epimer **9** was less effective than CPC **(7),** but it is not clear how the orientation of the

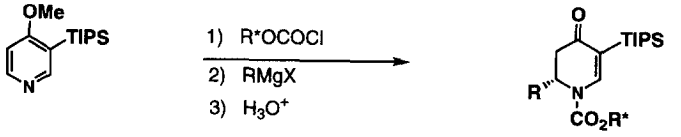


Table 1.

entry[a]	R*OCOCl (R*OH)	RMgX (R)	yield,[b] %	de[d,e]
a	**3**	*p*-Tol	89	89
b	**3**	*c*-Hex	95[c]	88
c	**4**	*p*-Tol	91	93
d	**4**	*c*-Hex	92[c]	86
e	**5**	*p*-Tol	93[c]	83
f	**5**	*c*-Hex	84	83
g	**6**	*p*-Tol	71	89
h	**6**	*c*-Hex	82	86
i	7	Ph	81	95
j	7	Bu-≡-	76	90
k	7	*p*-Tol	89	92
l	**8**	*c*-Hex	81	90
m	**8**	*p*-Tol	64	94
n	**8**	vinyl	75	90
o	**9**	*c*-Hex	80	85
P	**9**	*p*-Tol	95[c]	79
q	**10**	Ph	80[c]	4

[a] *The reactions were generally performed on a 0.5 mmol scale.* [b] *Unless indicated, the yield is of the major diastereomer isolated from radial PLC.* [c] *Yield of diastereomeric mixture isolated from radial PLC.* [d] The *diastereomeric excess (de) was determined by HPLC.* [e] *Satisfactory IR, ^1H and ^{13}C NMR, and microanalysis data were obtained for all products.*

isopropyl group effects the transfer of chirality. More interesting is the question as to why the presence of the C-4 isopropyl group in the CPC derivatives enhances the auxiliary's effectiveness as compared to the TCC-type alcohols. Favorable non-bonded steric interactions with the pyridinium salt do not appear to play a significant role as indicated by examination of molecular models and molecular mechanics (MMX) calculations. One possibility is that the conformation of the CPC auxiliary is effected by the C-4 substituent in a manner which allows a better π-π stacking interaction[9-11] of the aryl group of the auxiliary and the pyridinium ring of the 1-acyl salt.[1b] We are attempting to clarify the nature and role of this interaction through experimental, X-ray and computational studies.

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